M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 8, 1999

To: Dockets Management Branch (HFA-305)

From: Ted Sherwood
Management Analyst
Office of Generic Drugs

Subject: Presentation Regarding Human Generic Drugs to Docket 90S-0308

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: Application of ICH Stability Guidances to Currently Marketed Drug Products

Presented for: AAPS Workshop on Stability Practices in the Pharmaceutical Industry

Date Presented: March 29, 1999

Presented by: Kenneth J. Furnkranz

Number of Pages: 27

Ted Sherwood

Attachment

90S-0308

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AAPS Workshop on Stability Practices in the Pharmaceutical Industry

Application of ICH Stability Guidances to Currently Marketed Drug Products

Kenneth J. Furnkranz

Stability Technical Committee

Center for Drug Evaluation and Research

March 29, 1999

Stability Guidance

- Incorporates ICH Guidelines
  - **Q1A** - Stability Testing of New Drug Substances and Products
  - **Q1B** - Stability Testing: Photostability Testing of New Drug Substances and Products
  - **Q1C** - Stability Testing: Requirements for New Dosage Forms
  - **Q5C** - Stability testing of biotech/biological products

Stability Guidance

- **Uniform storage statements**
  - NDAs other than new molecular entities
  - Stability testing for ANDAs
  - Stability considerations for INDs
- **Reporting stability data**
- **Mean kinetic temperature**
  - Container/closure considerations

Stability Guidance

- Microbiological control and quality
- Stability sampling considerations
- Statistical considerations and evaluation

- **Bracketing and matrixing**

- Site-specific stability data
- Thermal cycling
- Stability testing in foreign laboratory facilities

Stability Guidance

- Stability considerations for specific dosage forms
- **Stability testing: post-approval changes**
- **Change in the stability protocol**
- **Application of Q1A to approved Drug Products**

Q1A Core Stability Package

Stability Storage Conditions

Condition	Temperature	Relative Humidity
Long-term Testing	25° C ± 2 °C	60% RH ±5% RH
Accelerated Testing	40° C ± 2 °C	75% RH ±5% RH
Intermediate Testing	30° C ± 2 °C	60% RH ±5% RH

Uniform Storage Statement

- Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F)

  [see USP Controlled Room Temperature]

- Store in a refrigerator, 2-8°C (36-46°F)

  or

  Store refrigerated

Uniform Storage Statement

- **USP DEFINITION OF CRT**
  - A Temperature maintained thermostatically that:
    - Encompasses the usual and customary working environment of 20º-25ºC
    - Results in a MKT calculated to be nmt 25ºC
    - Allows for excursions between 15º -30ºC
- **Articles may be labeled for storage at:**
  - Controlled Room Temperature
  - "Up to 25ºC"
  - "other wording" based on the same MKT

Mean Kinetic Temperature

- The isothermal temperature corresponding to the kinetic effects of a time-temperature distribution
- The single calculated temperature that simulates the non-isothermal effects of storage temperature variations
- Guidance provides instructions on how to calculate MKT and how to utilize MKT in determining the adequacy of a facility

Mean Kinetic Temperature

- FDA will accept various mechanisms
- Minimum of weekly High and Low readings
- More frequent readings recommended
- Individual Readings to be used (no averages)

Bracketing

- Applies to multiple sizes and strengths
- Applies to most types of drug products
- Container/closure of same composition
- Justification necessary
- If formulation varies, bracketing is not applicable
- Consult with appropriate Agency Review Division
- May be used pre- or post-approval
- Generally not applicable during IND

Matrixing

- Applies where multiple factors are evaluated
- Consultation with FDA is encouraged
- Applies to multiple sizes and strengths
- Applies to most types of drug products
- Batches, strengths with identical formulations, containers sizes, fill sizes, intermediate times
- Applicability to primary batches depends on product stability

Stability Testing for Post-approval Changes

- Change in manufacturing process for the drug substance
- Change in manufacturing site
- Change in formulation of the drug product
- Addition of a new strength for the drug product
- Change in manufacturing process and/or equipment for the drug product
- Change in batch size of the drug product
- Reprocessing of a drug product
- Change in container and closure of the drug product
- Change in the stability protocol

Stability Testing for Post-approval Changes

- Extent of stability data packages will depend on the potential for a change to affect a drug product's performance and the amount of experience an applicant has with a product
  - Amount of data with the submission
  - Post-approval commitment
  - Type of submission

Application of Q1A to Approved Drug Products

- Use of ICH condition for approved drug products is **voluntary** for either **Annual Batches** or Batches to support **Supplemental Changes**
- Switchover can be accomplished:
  - With approved protocol - annual report
  - Without approved protocol - PAS
  - Other changes to approved protocol via PAS
- Recommend comparison of data at currently approved storage conditions versus proposed ICH storage conditions

Switchover to ICH Conditions for Approved Drug Products: PLAN A

- For Drug Products where Stability is not expected to be affected by the new conditions:
  - Immediate Switchover.
  - Test only at ICH Condition
  - Three verification batches necessary

Switchover to ICH Conditions for Approved Drug Products: PLAN A

- **Satisfactory Data:**
  - Submit in Annual Report.
  - Keep same Expiration Date
- **Unsatisfactory Data:**
  - Investigate cause
  - Submit "Field Alert Report" or "Error & Accident Report"
  - Potential Voluntary Recall
  - Shorten Expiration date as appropriate (CBE Supp.)
  - Request specification changes/previous expiration date.
  - More protective c/c system or product reformulation
  - Switch back to non-ICH conditions.

Switchover to ICH Conditions for Approved Drug Products: Plan B

- For potential "Moisture Sensitive Products"
  - Perform Side-by-Side Studies (Approved Protocol vs ICH Condition [alternate protocol])
  - Three verification batches necessary

Switchover to ICH Conditions for Approved Drug Products: PLAN B

- Satisfactory Data: Submit in Annual Report. Keep same Expiration Date
- Unsatisfactory Data:
  - Adopt ICH condition & Shorten Expiration Date (CBE Supp.), or
  - Request specification changes/previous expiration date (PA Supp.)
  - More protective c/c system or product reformulation (PA Supp.)
  - Decide not to pursue ICH switchover.
- If product fails ICH and Non-ICH Conditions
  - Investigate cause, submit "Field Alert Report" or "Error & Accident Report", potential voluntary recall

Site Specific Stability Open Meeting:

- March 31, 1999
- 9:00 AM - 2:00 PM
- Holiday Inn Bethesda
  8120 Wisconsin Ave.
  (301) 652-2000

Call Kimberly Topper (301) 827-7001 by March 24th to present at the meeting

AAPS Workshop on Stability Practices in the Pharmaceutical Industry

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